REMARKS/ARGUMENTS

Reconsideration of the above-identified application respectfully requested.

In light of the Examiner's kind withdrawal of restriction and rejoinder of Groups 1, 2, and 13, Applicants have amended claim 57 to change the transitional phrase "comprising" to "consisting essentially of" so that the transitional phrase in claim 57 conforms with the transitional phrase of claim 1. This amendment is made for ministerial purposes only. No new matter is added by this amendment and entry of the amendment is respectfully requested. Accordingly, Applicants assert that no claims have been narrowed with the meaning of *Festo* (*Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 US 722, 112 S.Ct. 1831, 152 L.Ed.2d 944, 62 USPQ2d 1705 (2002)).

Applicants have made clear in the specification and through the claims under consideration that the instant invention is neither anticipated nor rendered obvious by any prior art, either alone or in combination. The Examiner states in explanation for each of the rejections of record that "[a]pplicants have not gone on the record stating unequivocally that proteins less than 50kDa in size are specifically excluded in the instant invention." (emphasis in original). It is noteworthy that the Examiner points to no passage in any of the cited art that specifically discloses or claims the Applicants' invention of a therapeutic factor possessing a size of greater than 50 kDa.

Both the specification and the claims make clear that Applicants consider their invention to consist essentially of *only* those components of the cellular supernatant from stimulated cells that are selected by an ultrafiltration membrane with a size exclusion limit of 50 kDa. Those components of the supernatant of cells stimulated according to the Applicants' Invention that are not selected by an ultrafiltration membrane with a size exclusion limit of 50 kDa are excluded from the claimed invention. That the factor may be a multimer based on a monomer of less than 50 kDa size is irrelevant since the active form of the material is greater than 50 kDa in size. Thus, Applicants' claims have also been limited to those components of the cellular supernatant from stimulated cells that do not pass through an ultrafiltration membrane with a size exclusion limit of 50 kDa. The claim language chosen by Applicants, *viz.*, "consisting essentially of", limits the scope of the claims to the specified materials or steps "and those that do not materially affect the basic and novel characteristics" of the claimed invention. *In re Herz*, 537 F.2d 549,551-552, 190 USPQ 461, 463 (CCPA 1976). Applicants, then, believe that the claims make

clear that *only* those components from mitogenically stimulated lymphocyte cells of greater than 50 kDa are part the claimed invention.

It is inappropriate to construe the transitional phrase "consisting essentially of" as equivalent to "comprising" in this instance, because those components of the cellular supernatant eliminated by the Applicants' invention by exclusion chromatography clearly do not have a material effect on the basic and novel characteristics of the claimed invention. The specification makes clear that the method of Applicants' invention is superior to the crude preparation disclosed in the art, namely the preparation of the Triozzi in U.S. Patent No. 6,093,381 (Triozzi '381). Applicants disclose in the specification numerous specific Examples that demonstrate the novel characteristics of their invention. Applicants draw the Examiner's attention in particular to Example 1 and Tables 1 and 4A; Example 5, Table 25; and Example 6, Table 27. Each of these tables report data to the effect that the presence of the greater than 50 kDa fraction displays superior results (*e.g.*, anti-viral activity and anti-tumor activity) compared to the less than 50 kDa fraction and greater than the entire supernatant of Triozzi '381. There can be no doubt that Applicants' invention is a material improvement over the crude preparation of the Triozzi '381 patent. When the claims under consideration are read in light of the specification, Applicants' invention is distinct from, and patentable over, any prior art, alone or in combination.

These data also bespeak of a lack of any double patenting allegations, because there is no way that the skilled artisan could possibly know what material in the crude Triozzi '381 preparation would exhibit superior activity compared to the entire supernatant, much less any certainty that any material therein would exhibit superior activity. Such is unsupported speculation on the part of the Examiner. Moreover, it is possible that fractionation of a supernatant, such as that of Triozzi '381, could destroy all activity.

No prior art either anticipates or makes obvious a factor specifically of greater than 50 kDa, derived from mitogenically stimulated lymphocyte cells, which factor is useful for treating patients afflicted with a disease that leads to an immunosuppressed state. Applicants' claimed factor simply was not in possession of the public prior to the instant invention, and no cited art describes a manner in which the claimed factor could be obtained.

Claims 1-8 and 57-66 have been rejected by the Examiner under 35 U.S.C. §102 as being anticipated by Triozzi '381. The Triozzi '381 patent does indeed disclose subject

matter that is broader than Applicants' invention. Nonetheless, Applicants have made a patentably distinct invention that could not be derived from the disclosure of the 'Triozzi '381 patent without extensive experimentation. In fact, there is no certainty that any amount of experimentation would reveal a Factor that would exhibit improved anti-viral and anti-tumor activity compared to the entire supernatant. Again, the Examiner is inherently making this assumption without a whit of support.

Applicants have disclosed extensive new matter in the instant application that describes the extensive experimentation necessary to enable those skilled in the art to determine that the active components of the supernatant are enriched in that fraction of greater than 50 kDa. The extensive experimentation necessary to make the determination of the relative size of the active factor is *prima facie* evidence that the Applicants' invention is neither anticipated by nor obvious from the Triozzi '381 patent.

The Triozzi '381 patent admits that the "molecular mechanisms underlying the interaction are not clear....[w]hether the effects are mediated by cytokines, however, has not yet been established in the literature, and it is possible that other soluble mediators are operational." (Col. 4, ll. 1-2, ll. 19-22). The Triozzi '381 patent does not disclose a composition or size of the active components of the stimulated cell supernatant, and the Examiner does not point out any specific language in Triozzi '381 that anticipates or makes obvious Applicants' instant invention. For these reasons, the Triozzi '381 patent does not anticipate the claims and Applicants request that the 35 U.S.C. §102 rejections be withdrawn.

Claims 1, 5, 57, and 61 have been rejected by the Examiner under 35 U.S.C. §102(b) as being anticipated by Chang *et al.* U.S. Patent No. 4,596,774 (Chang '774). For the same reasons stated above, and in prior responses before the Examiner, Applicants disclosed invention claims matter not disclosed or enabled by the Chang '774 patent. The Chang '774 patent discloses and claims a rather crude method for producing monoclonal antibodies in a cell culture system supplemented with mouse serum. (*See* the only independent claims in Chang '774: Claim 1, col. 11, l. 63; Claim 13 Col. 12, ll. 52-53.) Unlike Chang '774, Applicants preferred embodiment proliferates cells in serum free media. Nor is the method of mitogenic stimulation disclosed by Applicants disclosed by Chang '774. In the instant application, both the specification and the claims make clear that Applicants consider their invention to consist essentially of *only* those components of the cellular supernatant from stimulated cells that are selected by an ultrafiltration membrane with a size exclusion limit of 50 kDa. Applicants' invention is neither disclosed nor enabled by

Chang '774, and the Examiner has not specifically cited any disclosure to support such an inference. Therefore Applicants request that the Examiner's rejection be withdrawn.

Claims 1-3 and claims 57-59 have been rejected by the Examiner under 35 U.S.C. §102(b) as being anticipated by Triozzi *et al.* (*Aids Res. and Human Retroviruses*, Vol. 14, No. 8, 1998) (Triozzi *et al.*, 1998). The Examiner does not cite a disclosure in this paper by Triozzi of the characterized fraction that Applicants claim, nor does any such disclosure exist. Those skilled in the art could not identify a particular fraction that was capable of therapeutic benefit without extensive experimentation. Triozzi *et al.*, 1998 expressly admit lack of knowledge of any therapeutic activity *in vivo*, stating "[n]onetheless, the chemokine-releasing cells expanded in these short-term cultures *ex vivo* may be sufficient to be applied therapeutically as an autologous cellular therapy for HIV-1. The effects of these cells, and whether their infusion can augment a response that is obviously incomplete *in vivo*, are currently under clinical investigation." (Triozzi *et al.*, 1998, p. 648). There is no suggestion of any kind in the Triozzi *et al.*, 1998 citation of any particular size of component of the supernatant that might possibly comprise the active component. The express language of Triozzi *et al.*, 1998 makes clear that the authors do not have any clear and definite idea that the supernatant might be effective for treating patients. The concluding sentences of Triozzi *et al.*, 1998 simply suggest an approach that is obvious to try. There are no identified criteria in Triozzi *et al.*, 1998 that suggest any prediction of the level of experimentation required or of the likelihood of success.

Extension of Time

In order to permit the examiner to fully consider Applicants response, Applicants submit herewith a request for a one-month extension of time up to and including July 11, 2003 to file a notice of appeal.

Conclusion

In light of the novel and nonobvious inventive matter disclosed by the application, Applicants kindly request the Examiner withdraws the rejections of record. Accordingly, in view of the Applicants' current and previous amendments to the claims and remarks submitted herewith, allowance of all claims and passage to issue of this application respectfully is requested. If an allowance is not forthcoming, please enter this amendment for purposes of appeal. Should any questions remain, the Examiner respectfully is invited to telephone the undersigned.

Appln. No. 09/727,198
After Final Amendment dated June 25, 2003
Reply to Final Office Action of March 11, 2003

Respectfully submitted,

Date: 25 June 03

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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this Response After Final (BOX AF) is being sent on June 25, 2003, by facsimile to the Honorable Commissioner of Patents at facsimile number 703-872-9307 as an after final communication.

Jane Keeney